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| EXAMINER | |
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| YAO, LEI | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/724,983 | WALDMAN, SCOTT A. | |
| | Examiner | Art Unit | |
| | Lei Yao, Ph.D. | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☐ Claim(s) *23,28-30,36 and 50-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,28-30,36 and 50-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Arguments*

The Remarks filed on 10/31/2007 in response to the previous Non-Final Office Action (5/1/2007) is acknowledged and has been entered.

Claims 23, 28-30, 36, and 50-89 are pending and under consideration.

***Claim Objection***

Claims 23, 28, 50-60, 63, 64, 68-78, 81-84 are objected to because of the following informalities: The specification provides definition of term "ST" as heat-stable toxin and ST receptor as the receptors found on colorectal cells (page 5 and 6). However, the abbreviation "ST receptor" should be spelled out when first used in the claims. Appropriate correction is required.

***Rejection Maintained-Double Patenting***

1. Claims 23, 28-30, 36, and 50-89 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 9, 10, 28-31, and 54-58 of U.S. Patent No. 5,879,656

2. Claims 23, 28-29, 58, 63-65, 76, 81, 82, and 85 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6 and 8 of U.S. Patent No. 6060037 in view of de Sauvage et al., (JBC, vol 267, page 6479-6482, April, 1992).

For the rejections above, applicant indicates that a Terminal Disclaimer will be filed when the claimed subject matter is allowable (page 9-10). Thus, rejections are maintained for reason of the record and made again here as set forth in the Office action dated on 5/1/2007.

***Rejection Maintained and Response to Arguments***

***35 USC § 112-2nd Paragraph***

The following is a quotation of the **second paragraph of 35 U.S.C. 112**:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23, 28-30, 36, and 50-89 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as stated the following:

Claims are indefinite because the term "a therapeutically effective amount of pharmaceutical composition or conjugated compound that comprise an ST receptor ligand wherein said ST receptor ligand is an antibody, Fab or $F(AB)_2$" in claim 23, 63, and 81 is not clear.
MPEP2173.05 state:

> *The common phrase" an effective amount" may or may not be indefinite. The proper test is whether or not one skilled in the art could determine specific values for the amount based on the disclosure.*
>
> *The phrase "an effective amount" has been held to be indefinite when the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art. In re Fredericksen 213 F.2d 547, 102 USPQ 35 (CCPA 1954).*

The specification on page 37 teach that "A therapeutically effective amount" is an amount which is effective to cause a cytotoxic or cytostatic effect on metastasized colorectal cancer cells without causing lethal side effects on the individual. However it does not teach what has been achieved in the treatment or whether the amount of the antibody used in the treatment is "therapeutically effective amount". Therefore, the metes and bounds of "a therapeutically effective amount" in claims 23 and 63 cannot be determined because those skilled in the art would not be able to determine the therapeutically effective amount of the ST receptor antibody used for claimed method. Claims 23 and 63 also render the dependent claims indefinite.

Response to Applicant's Argument:

The response filed 10/31/2007 has been carefully considered but is deemed not to be persuasive.

At page 2-3, applicant states:

> The claims make clear the meaning of "a therapeutically effective amount." ....In each of claims 23, 63 and 81, the claim recites that the active agent "causes cell death, inhibits cell division or induces differentiation".
>
> The specification provides further evidence of the clear meaning of "a therapeutically effective amount."
> state:" ...methods for specifically targeting and eliminating metastasized colorectal cancer cells"....and "methods for specifically eliminating colorectal cancer cells".
>
> "A therapeutically effective amount is an amount which is effective to cause a cytotoxic or cytostatic effect on metastasized colorectal cancer cells without causing lethal side effects on the individual"
>
> "...Here, the function to be achieved is to eliminate metastasized colorectal cancer cells by cytotoxic or cytostatic effect, without lethal side effects"

In response, the indefinite rejection of claims here is based on the unclear recitation of "a therapeutically effective amount " of ST receptor ligand or antibody, not an active agent (second agent) in the

composition recited in claimed method. Claims 23, 63 and 81 reciting that an active agent causes cell death, inhibits cell division, or induces differentiation do not define the effective amount of ST receptor ligand comprising antibody in pharmaceutical composition because the functional language only refers to the active agent, not the ST receptor ligand, in the composition. The active agent as a part of the claimed composition has been further limited as a chemotherapeutic agent in claim 30, 66, and 88, which is well known and used in the art. In addition, the specification as stated above does not define "a therapeutically effective amount" of ST receptor ligand comprising antibody either. "the cytotoxic or cytostatic effect" of the composition seems to refer to the active agent (chemotherapeutic agent) in the composition because the specification does not provide any teaching on any ST receptor ligand having cytotoxic or cytostatic effect on the metastatic colon cancer cells. Thus, applicant's argument has not been found persuasive, and the rejection is maintained for reason of the record.

***35 USC § 112-1st Paragraph-Enablement***

The following is a quotation of the **first paragraph of 35 U.S.C. 112:**

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 28-30, 36, and 50-89 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention as stated the following:

The claims are drawn to a method of treating an individual suspected of suffering, or suffering from metastatic colorectal cancer comprising the step of administering to individual pharmaceutical composition comprising an active agent comprising 5-fuorouracil and an ST receptor antibody, Fab or $F(AB)_2$. To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provides an enabling disclosure of how to make and use a claimed invention. The method objective of claims is a method of treating a colorectal cancer with a composition comprising an antibody to ST receptor. Thus, it would be expected that one of skill in the art would be able to treat the cancer with any antibody to receptor without undue experimentation by using the claimed method.

The specification teaches heat stable toxin referred as ST or ST receptor binding peptide or ST peptide (page 13). The specification teaches ST receptors are unique in that they are only localized in the apical brush border membranes of the cells lining the intestinal tract (bridge pate of 9-10). The specification teaches Guanylin, a 15 amino acid peptide, has about 50% sequence homology to ST and

binds to ST receptor and activates guanylate cyclase (page14). The specification further teaches that an assay may be use to determine whether or not the peptides are ST receptor ligands comprising incubating a preparation of ST receptor (intestinal membranes from rat or human intestine or the cells, page 17). However, the specification does not provide teachings on A) the detailed information about the ST receptor expressed in the colorectal cancer cells comprising structure or sequence; B) antibody to the ST receptor interacting with the ST receptor on colorectal cancer; C) the method of treating any cancer with the composition comprising antibody to the ST. Thus, the specification invites the skilled artisan to experiment to determine how to use the claimed composition comprising an ST receptor antibody or the Fab or F(ab)2 to treat metastatic colorectal cancer does not set forth sufficient teachings to allow one skilled in the art to practice treating such cancer. There are no working examples to guide or assist the skilled artisan in practicing the claimed method of treating metastatic colorectal cancer with antibody or antibody fragment in combination with other active agent. In addition, although the specification cites a few references (page 15) teaching the ST binding, non of the references identify or teach the ST receptor. For example, a cited reference, (Okamoto, Infec and Immun vol 55, page2121-2125, 1987), on line 32 of page 15, teaches that ST receptor is separable from guanylate cyclase indicating that the receptor is coupled to the activation of guanylatd cyclase (page 2124, col 1 and cited reference 11, abstract) and reference does not suggest or teach what the receptor is. Thus, one skilled in the art and specification did not seem have identified the ST receptor with a sequence expressed on colorectal cancer cells at the time of filing instant application. Therefore, the specification provides insufficient guidance or direction to predictably enable one of ordinary skill in the art to use the claimed invention to treat colorectal cancer with composition or conjugate comprising antibody to ST receptor.

Moreover, those of skill in the art recognize the unpredictability of treating tumors with antibodies. The references have been discussed in the previous office action and again below.

Jain R. K. (Scientific American, 271(1): 58-65, July 1994) discloses the art known barriers to the delivery of drugs into solid tumors. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutic molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). Further, Dillman R. O., (Annals of Internal Medicine, 111:592-603, 1989) summarizes (see abstract) the status of in-vivo use of monoclonal antibodies for treating cancer wherein despite advances in biotechnology, many major hurdles persist including tumor cell heterogeneity, lack of cytotoxicity, and the development of human anti-mouse antibodies (HAMA). Also, Weiner L. M. (Seminars in Oncology, 26 (4 Suppl 12):41-50, August 1999) provided an overview of monoclonal antibody therapy including some promising activity, however, major obstacles to clinical efficacy still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets and insufficient target specificity (see page 43).

Furthermore, as disclosed by Dillman, R. O. [b] (Journal of Clinical Oncology, 12(7):1497-1515, 1994) discloses, after reviewing the literature on the use of unconjugated monoclonal antibodies to treat cancer, that "at present, there are no unconjugated monoclonal antibodies that have proven therapeutic benefit in hematologic malignancies or solid tumors." Thus, absent objective evidence to the contrary, it is highly unpredictable that applicant's unconjugated antibody would possess any therapeutic effects for colorectal cancer.

No direction or guidance is provided in current specification to assist one skilled in the art using a composition comprising an antibody to ST receptor or its fragment that in a method of treating colorectal cancer. In view of the lack of the predictability of the art to which the invention pertains as evidenced by the art above, one skilled in the art would be forced into under experimentation in order to practice the claimed invention.

Previous response to applicant's argument dated 8/23/2006 is also maintained for reason of the record as set forth in the Office action dated 5/1/2007.

Response to applicant's argument dated on 10/31/2007

The response has been carefully considered but is deemed not to be persuasive.

At page 5, applicant states:

> The claims are enabled because the combination of the specification and the knowledge of one of skill in the art, to practice the claims would only require routine experimentation, not undue experimentation. The pending claims are directed to methods of treating metastatic colorectal cancer cells, i.e. causing the cells to stop growing or to kill them without causing lethal side effects in the individual. These methods are employed by using the expression of the ST receptor on the colon cancer cells as a target for the binding moiety or antibody, Fab, or Fab2. The ability of the ST receptor to be used as the target allows for greater specificity in treatment without the unwanted side effects of non-specific cancer treatments, such as traditional chemotherapeutics that affect every cell not just a sub-class of cells. The present application identified that an important target that can be used for treating metastatic colon cancer is the ST receptor.

In response, applicant is reminded that claimed invention is drawn to a method for treating an individual with metastatic colorectal cancer, which requires allowing one skilled in the art to practice claimed invention without under quantity of experimentation. However, neither the instant specification, nor the art of record has described or suggested such method. Although applicant has established the initial concept for the claimed method as stated in the rejection, which is merely an invitation for the skilled artisan to the experimentation to determine whether the composition comprising ST receptor ligand, or antibody could be used or how to use in vivo for the treatment because applicant does not provide objective evidence, direction/guideline showing that the concept has worked and allows claimed invention to be practice in an individual without undue experimentation. Again, as stated in the rejection, application does not provide enough teaching on the expression of the ST receptor on the metastatic colon cancer cells, which contributes to the colon cancer metastasis and as such, treating the cancer with a ligand of ST receptor or antibody would be unpredictable. Thus, even to the one of skilled in the art, the

experimentation would not be routine, but undue to determine whether the ligand of or antibody to the ST receptor could perform the claimed function before claimed invention could be practiced in the individuals.

At bridging page 5-6, applicant again argues the references cited in the office action, which has been discussed in the previous office action and again in the rejection above. In fact, all the references have one major concern for treating cancer in vivo with drug of large molecules, such as antibodies, which is involved in clinical efficacy of treatment that can be only overcome by providing objective evidence showing that the antibody or the molecule does work and has the claimed effect. Instant application does not provide such evidence to convince one skilled in the art that claimed method could work as claimed and as concerned in the references. At page 6, applicant further argues the enablement of humanized antibody for treatment of a cancer in the art, which is not concerned in this application because if application provides objective evidence that claimed method works in vivo, such as in mice with mouse antibody, which would be generally considered enabled in an individuals for the instant method as claimed and because making humanized antibody is well known technology.

At page 6-7, applicant provides a few publications as examples for treating cancer comprising colon cancer with antibodies and argues that current technology of targeting cancer cell based on the receptor expressing on the cell surface are enabled (not a nascent technology). Then, at bridging page 7-8, applicant states:

> the present application teaches the novel and non-obvious use of the ST receptor to target metastatic colon cancer cells, which is the "aspect of the invention that one of skilled in the art could not figure out without undue experimentation." The application need not teach the general methods of administering a composition as claimed because that is something one of skill in the art could already "figure out" without undue experimentation.

In response, the Office agrees that there are many enabled disclosure including publications and patents in the field for treating a cancer comprising colon cancer with an antibody for targeting the surface expressed antigen in the cancer cells and there are numbers of antibodies having used in clinic for treating a cancer. Applicant may have noticed that each and every single document has provided objective evidence, such as experimentations or examples to support claimed or disclosed method that actually works for such treatment. However, instant application only contemplates the method based on

the possible ST receptor expressed in apical membrane on the sides of the intestinal cells and neither detailed structure, nor amino acid sequence for the ST receptor is disclosed in this application and no experimentation is performed and no treatment result is described. Thus, although one skilled in the art need not teach the general method of administering the composition as claimed as stated above, the skilled artisan would like to know that the composition has been tested and worked for treating or inhibiting colon cancer cell metastasis before they actually is administered to an individual having the metastatic colon cancer for the treatment.

"Undue experimentation" has been interpreted as require that the claimed invention be enable so that any person skilled in the art can make and use the invention without undue experimentation. "Test of enabled is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation." (see MPEP 2164.01).

According to the MPEP and response as set forth above, claimed invention is obviously not enabled.

At page 8-9, based on not providing the structure of ST receptor in the rejection, applicant further argues that ST receptor had been characterized at the time the present application was filed and also cited a few references that identified the bacterial heat-stable toxin receptors by binding of peptide toxin to the cell surface. Finally, applicant concludes that it is clear that the identity of the protein referred to in the specification as the 'ST receptor' was known to one of skill in the art at the time the invention was made and that those skilled in the art would only need routine experimentation to raise antibodies or develop other binding partners against the protein.

In response, first, as stated above, although raising antibodies to a known protein or developing binding partner against the protein is known technology and considered as a routine experimentation, applicant is reminded that claimed invention is NOT drawn to products, antibodies or binding partners to an known ST receptor, instead, the application claims a method of treating colon cancer with an antibody or binding partner, which is NOT routine, but requires undue quantity of experimentations since application does not show objective evidence and no guideline/direction indicating that the antibody or binding partner to ST receptor would work as claimed. Again, one skilled in the art would clearly know treating cancer with antibody or receptor binding partner is NOT predictable and would require intensive research and undue quantity of experimentations before practice of the method in individuals with the

diseases. Second, the term "ST" defined as heat-stable toxin is a broad term, which reads on any heat-stable toxin with different structures from different sources as defined in NCBI Mesh word search result (see attached). Each toxin having different structure and sequence would bind to its own receptor with unique structure and sequence. Claimed invention is drawn to a method of treating a metastatic colorectal cancer comprising administering an ST receptor ligand comprising antibody to ST receptor, which would require showing which ST receptor refers to and what the structure of the receptor is in order to allow one skilled in the art to make and use the method.

Thus, in view of the response above and in previous office action dated on 5/1/2007, the Office has provided enough evidence indicating that the claimed method is not enabled at time of filing the application and would require undue experimentation in order to use the method by one skilled in the art. Thus, applicant's argument has not been found persuasive, and the rejection is maintained.

***Conclusion***

No claim is allowed.

**THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

LY

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER